Seponering versus fortsat behandling med antipsykotika af demente patienter – en gennemgang af et Cochranereview

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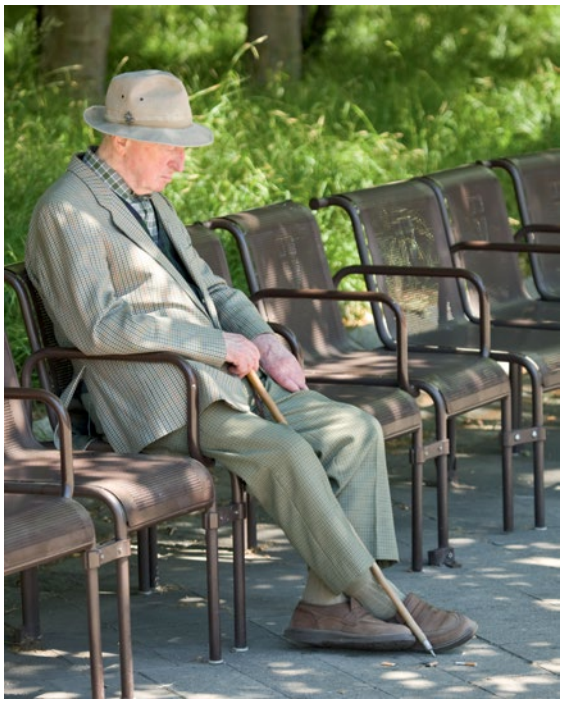
Der er stigende fokus på demenssygdomme. Ifølge Nationalt Videnscenter for Demens lever ca. 85.000 med en demenssygdom, og dette tal vil stige i de kommende år i takt med det stigende antal ældre på grund af de store årgange efter 2. verdenskrig og den øgede middellevetid. I 2030 forventes antallet af personer med demens i Danmark at være steget til ca. 130.000. Der er store social- og sundhedsudgifter forbundet med behandling af personer med demens. Den gennemsnitlige udgift pr. person estimeres at ligge på 100.000-112.000 kr. pr. år. Heraf er 26% direkte sundhedsudgifter, og de sociale (kommunale) udgifter primært i form af pleje og omsorg udgør ca. 74%. Samlet anslås de direkte omkostninger at beløbe sig til mindst 8,7 mia. kr. årligt. Derudover yder pårørende en ganske betydelig pleje- og omsorgsindsats. Sundhedsstyrelsen har til brug for udredning og behandling af demens udarbejdet en national klinisk retningslinje, der udkom i efteråret 2013 [1].

Demenssygdommenes invaliderende karakter skyldes ikke kun de kognitive forstyrrelser, men også i høj grad de psykiatriske symptomer og adfærdsforstyrrelser, der opstår i sygdomsforløbet. I den internationale litteratur kaldes symptomerne *behavioural and psychological symptoms of dementia* (BPSD). BPSD omfatter bl.a. apati, depression, angst, hallucinationer, vrangforestillinger, agitation, verbal eller fysisk aggression, handletrang, omkringvandring, råben, uhæmmethed samt spise- og søvnforstyrrelser. Symptomerne opstår i et samspil mellem demenssygdommen, patienten og miljøet. Hyppigheden af BPSD varierer betydeligt, men mere end halvdelen af patienter med en demenssygdom får sværere BPSD især i de senere stadier af demenssygdommen. Symptomerne, specielt svær agitation/aggression samt vrangforestillinger og hallucinationer, er meget belastende, ikke mindst for pårørende og plejepersonale.

Ikkefarmakologisk behandling anbefales som førstevalg ved behandling af BPSD. Det forudsættes, at pleje, omsorg og aktiviteter rettet mod personer med demens tilrettelægges individuelt, baseret på kendskab til den enkelte patient, og i Sundhedsstyrelsens kliniske retningslinje anføres, at pleje baseret på en socialpædagogisk struktureret praksis kan mindske risikoen for udvikling af adfærdsforstyrrelser [1]. Ved undersøgelser af farmakologisk behandling af BPSD ses ofte en betydelig placeboeffekt som følge af, at patienterne får øget opmærksomhed [2]. Farmakologisk behandling med kolinesterasehæmmere kan muligvis have en mindre effekt på BPSD, og memantin synes ligeledes at have en beskeden effekt. I en nyligt publiceret undersøgelse af memantin til behandling af svær agitation var effekten af stoffet imidlertid ikke bedre end effekten af placebo [3]. Antipsykotika anvendes ofte til behandling af BPSD, selvom effekten er begrænset, og der er risiko for betydelige bivirkninger bl.a. sedation, ekstrapyramidale symptomer, tardive dyskinesier, vægtøgning og metabolisk syndrom foruden øget hyppighed af apopleksi og øget dødelighed.

I en oversigtsartikel fra 2011 konkluderede *Ballard et al*, at risperidon og aripiprazol havde en begrænset effekt i op til 12 uger på aggression og psykose, at olanzapin havde en ikkeoverbevisende effekt på agitation, samt at quetiapin ingen effekt havde



Hos mange demente patienter kan behandlingen med antipsykotika seponeres.

ABSTRACT

Withdrawal versus continuation of chronic antipsychotic drugs for behavioural and psychological symptoms in older people with dementia

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BACKGROUND

Antipsychotic agents are often used to treat neuropsychiatric symptoms (NPS) in dementia, although the literature is sceptical about their long-termuse for this indication. Their effectiveness is limited and there is concern about adverse effects, including highermortality with long-term use. When behavioural strategies have failed and drug therapy is instituted, regular attempts to withdraw these drugs are recommended. Physicians, nurses and families of older people with dementia are often reluctant to try to stop antipsychotics, fearing deterioration of NPS. Strategies to reduce antipsychotic use have been proposed, but a systematic review of interventions aimed at withdrawal of antipsychotic agents in older people with dementia has not yet been performed.

OBJECTIVES

To evaluate whether withdrawal of antipsychotic agents is successful in older people with dementia in community or nursing home settings, to list the different strategies for withdrawal of antipsychotic agents in older people with dementia and NPS, and to measure the effects of withdrawal of antipsychotic agents on behaviour.

SEARCH METHODS

ALOIS, the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG), The Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS, clinical trials registries and grey literature sources were searched on 23 November 2012. The search included the following terms: antipsychotic* or neuroleptic* or phenothiazines or butyrophenones or risperidone or olanzapine or haloperidol or prothipendyl or methotrimeprazine or clopenthixol or flupenthixol or clothiapine or metylperon or droperidol or pipamperone or benperidol or bromperidol or fluspirilene or pimozide or penfluridol or sulpiride or veralipride or levosulpiride or sultopride or aripiprazole or clozapine or quetiapine or thioridazine combined wither terms such as discontinu* or withdraw* or cessat* or reduce* or reducing or reduct* or taper* or stop*. ALOIS contains records from all major healthcare databases (The Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS), as well as from many clinical trials registries and grey literature sources.

SELECTION CRITERIA

Randomised, placebo-controlled trials comparing an antipsychotic withdrawal strategy to continuation of antipsychotics in people with dementia.

DATA COLLECTION AND ANALYSIS

Review authors independently assessed trials for inclusion, rated their risk of bias and extracted data.

MAIN RESULTS

We included nine trials with 606 randomised participants. Seven trials were conducted in nursing homes, one trial in an outpatient setting and one in both settings. In these trials, different types of antipsychotics prescribed at different doses were withdrawn. Both abrupt and gradual withdrawal schedules were used. The risk of bias of the included studies was generally low regarding blinding and outcome reporting and unclear for randomisation procedures and recruitment of participants. There was a wide variety of outcome measures. Our primary efficacy outcomes were success of withdrawal (i.e. remaining in study off antipsychotics) and NPS. Eight of nine trials reported no overall significant difference between groups on the primary outcomes, although in one pilot study of people with psychosis and agitation that had responded to haloperidol, time to relapse was significantly shorter in the discontinuation group (Chi2 = 4.1, P value = 0.04). The ninth trial included people with psychosis or agitation who had responded well to risperidone therapy for four to eight months and reported that discontinuation led to an increased risk of relapse, that is, increase in the Neuropsychiatric Inventory (NPI)-core score of 30% or greater (P value = 0.004, hazard ratio (HR) 1.94, 95% confidence interval (CI) 1.09 to 3.45 at four months). The only outcome that could be pooled was the full NPI-score, used in two studies. For this outcome there was no significant difference between people withdrawn from and those continuing on antipsychotics at three months (mean difference (MD) -1.49, 95% CI -5.39 to 2.40). These two studies reported subgroup analyses according to baseline NPI-score (14 or less versus > 14). In one study, those with milder symptoms at baseline were significantly less agitated at three months in the discontinuation group (NPI-agitation, Mann-Whitney U test z = 2.4, P value = 0.018). In both studies, there was evidence of significant behavioural deterioration in people with more severe baseline NPS who were withdrawn from antipsychotics (Chi2 = 6.8; P value = 0.009 for the marked symptom score in one study). Individual studies did not report significant differences between groups on any other outcome except one trial that found a significant difference in a measure of verbal fluency, favouring discontinuation. Most trials lacked power to detect clinically important differences between groups. Adverse events were not systematically assessed. In one trial there was a non-significant increase in mortality in people who continued antipsychotic treatment (5% to 8% greater than placebo, depending on the population analysed, measured at 12 months). This trend became significant three years after randomisation, but due to dropout and uncertainty about the use of antipsychotics in this followup period this result should be interpreted with caution.

AUTHORS' CONCLUSIONS

Our findings suggest that many older people with Alzheimer's dementia and NPS can be withdrawn from chronic antipsychotic medication without detrimental effects on their behaviour. It remains uncertain whether withdrawal is beneficial for cognition or psychomotor status, but the results of this review suggest that discontinuation programmes could be incorporated into routine practice. However, two studies of people whose agitation or psychosis had previously responded well to antipsychotic treatment found an increased risk of relapse or shorter time to relapse after discontinuation. Two other studies suggest that people with more severe NPS at baseline could benefit from continuing their antipsychotic medication. In these people, withdrawal might not be recommended.

sammenlignet med placebobehandling [4]. I en enkelt dobbeltblindet, placebokontrolleret undersøgelse af langtidsbehandling med antipsykotika i op til et år sås der ingen signifikant bedre effekt af antipsykotika end af placebo [5]. Ifølge beregning fra Lægemiddelstyrelsen fik 19% af de 65+-årige, der i 2009 var i behandling med demenslægemidler, samtidig behandling med antipsykotika [1].

I nærværende Cochranereview undersøges effekten af dobbeltblindet, placebokontrolleret seponering af antipsykotika hos demente patienter, der har været i behandling i mindst tre måneder. Der blev i perioden 1997-2012 inkluderet i alt ni undersøgelser, som omfattede 606 patienter. Hovedparten af studierne drejede sig om plejehjemsbeboere. De primære effektmål blev defineret som evnen til at gennemføre undersøgelsen uden dropout eller forværring af BPSD efter henholdsvis fire uger og tre måneder.

I syv af de ni undersøgelser var det muligt at seponere antipsykotika uden en signifikant effekt på de fleste effektmål. I et mindre pilotstudie af haloperidol, hvor man kun inkluderede patienter, der primært havde haft god effekt af haloperidol, var tiden til recidiv dog kortere for placebo end for fortsat behandling med haloperidol [6]. Det sidst publicerede studie fra 2012 inkluderede kun patienter, der havde Alzheimers sygdom, og som havde responderet på behandling af psykotiske symptomer eller agitation med risperidon i 16 ugers åben behandlingsperiode [7]. Efterfølgende blev patienterne dobbeltblindet randomiseret til fortsat behandling med risperidon i 32 uger, behandling med risperidon i 16 uger efterfulgt af 16 ugers placebobehandling eller 32 ugers placebobehandling. Resultaterne viste, at patienter, som havde psykotiske symptomer eller agitation og havde responderet på risperidon, havde en betydelig øget risiko for tilbagefald ved ophør af behandling med risperidon [7].

Det kan konkluderes, at behandlingen med antipsykotika kan seponeres hos mange patienter med demens. Hos en mindre gruppe, hvor der primært har været en effekt på psykotiske symptomer eller agitation/aggression, vil seponering medføre recidiv af symptomerne. Det er imidlertid ikke muligt at udpege disse patienter, og der bør derfor rutinemæssigt indgå planlægning af seponering af antipsykotika hos demente patienter, der sættes i antipsykotisk behandling, hvilket også er en klar anbefaling i Sundhedsstyrelsens retningslinje. Mange af patienterne sættes i behandling af gerontopsykiatriske/geriatriske team eller demensklinikker. Det ville være ideelt, hvis der altid blev forsøgt seponering af antipsykotika, mens patienten var i behandling i sekundærsektoren. Behandlingen af mange af patienterne vil imidlertid blive videreført af egen læge, hvorfor seponering af antipsykotika også vil blive en opgave for den praktiserende læge i et tæt samarbejde med pårørende, hjemmepleje og kommunale demenskoordinatorer.

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